

Acute bacterial meningitis in adults

Fiona McGill, Robert S Heyderman, Stavros Panagiotou, Allan R Tunkel, Tom Solomon



Summary

Over the past several decades, the incidence of bacterial meningitis in children has decreased but there remains a significant burden of disease in adults, with a mortality of up to 30%. Although the pathogenesis of bacterial meningitis is not completely understood, knowledge of bacterial invasion and entry into the CNS is improving. Clinical features alone cannot determine whether meningitis is present and analysis of cerebrospinal fluid is essential for diagnosis. Newer technologies, such as multiplex PCR, and novel diagnostic platforms that incorporate proteomics and genetic sequencing, might help provide a quicker and more accurate diagnosis. Even with appropriate antimicrobial therapy, mortality is high and so attention has focused on adjunctive therapies; adjunctive corticosteroids are beneficial in certain circumstances. Any further improvements in outcome are likely to come from either modulation of the host response or novel approaches to therapy, rather than new antibiotics. Ultimately, the best hope to reduce the disease burden is with broadly protective vaccines.

Burden of disease and epidemiology

The incidence of bacterial meningitis varies throughout the world. In the UK and western Europe, the incidence is 1–2 cases per 100 000 people per year, whereas it can reach 1000 cases per 100 000 people per year in the Sahel region of Africa (figure 1).^{1–3} A huge reduction in incidence has occurred over the past few decades, largely secondary to the introduction and widespread use of conjugate vaccines.^{1,3–6} Conjugate vaccines have a protein attached to purified bacterial capsular polysaccharide. This elicits a more robust and sustained immune response, especially in young children. Table 1 gives an overview of vaccines currently available to prevent bacterial meningitis. Much of the reduction in incidence has been in children younger than 1 year.^{1,5} Similarly, the largest reductions in meningitis-associated mortality, globally, have occurred in children younger than 5 years of age, with a 43% decrease in neonates and a 54% reduction in children aged 1–59 months.⁷ For those older than 5 years, the number of deaths globally only reduced by 2·7%, from 165 900 to 161 500 between 1990 and 2013.⁷

Streptococcus pneumoniae

Pneumococcus is the commonest cause of bacterial meningitis in adults in much of the world.^{1,5,8,9} There are more than 90 antigenically different serotypes of *S pneumoniae* as determined by the polysaccharide capsule; the target for all currently licensed vaccines.

Pneumococcal conjugate vaccines (PCV) have been used for the past 15 years. PCV7 targeted seven pneumococcal serotypes and more recently PCV10 and PCV13 (covering ten and 13 serotypes, respectively) were licensed in the USA and Europe. The polysaccharide vaccine PPV23 covers 23 serotypes. Until recently, conjugate vaccines were largely used only in children but a recent placebo-controlled trial¹⁰ in people aged 65 years and older has shown good efficacy of PCV13 in preventing vaccine-type pneumococcal pneumonia, non-bacteraemic pneumonia, and invasive pneumococcal disease, with vaccine efficacies of 46%, 45%, and 75%, respectively. Although most studies on the immunogenicity of

pneumococcal vaccines are non-comparative, there is some evidence that PCV is more immunogenic than polysaccharide vaccine.¹¹ The conjugate vaccines also produce substantial herd immunity, when vaccination of part of the population provides protection for non-vaccinated individuals. Large studies have shown substantial reductions of disease caused by vaccine serotypes in both vaccinated and unvaccinated populations.^{12–15}

Since conjugate vaccines were first introduced, serotype replacement has been reported. This is an increase in the incidence of disease or asymptomatic carriage caused by non-vaccine serotypes.^{16–19} However, the overall incidence of invasive pneumococcal disease has dropped. A meta-analysis from Europe, the Americas, and Australia showed a sustained reduction in the incidence of pneumococcal meningitis in children 7 years after vaccination (risk ratio for meningitis was 0·40, 95% CI 0·25–0·64). There was a similar, but smaller, reduction in adults with a relative risk of meningitis in 18–49-year-old people of 0·61 (95% CI 0·40–0·95) 7 years after vaccination. For adults aged 50–64 years, there was a decrease in meningitis caused by the vaccine serotypes but this was offset by a significant increase in non-vaccine serotype disease (rate ratio 2·83, 95% CI 1·46–5·47).²⁰ Mathematical models have

Published Online

June 2, 2016

[http://dx.doi.org/10.1016/S0140-6736\(16\)30654-7](http://dx.doi.org/10.1016/S0140-6736(16)30654-7)

Institute of Infection and Global Health, University of Liverpool, Liverpool, UK

(F McGill MBChB, S Panagiotou PhD, Prof T Solomon PhD);

Malawi-Liverpool-Wellcome Trust, Clinical Research Programme, University of Malawi College of Medicine, Blantyre, Malawi

(Prof R S Heyderman FRCP); Warren Alpert Medical School, Brown University, Providence, RI, USA (Prof A R Tunkel MD);

The Walton Centre NHS Foundation Trust, Liverpool, UK (Prof T Solomon); NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, Liverpool, UK

(F McGill, Prof T Solomon); Leeds University Hospitals NHS Trust, Leeds, UK (F McGill);

Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK (F McGill, Prof T Solomon); and Division of Infection and Immunity, University College London, London, UK

(Prof R S Heyderman)

Correspondence to Prof Tom Solomon, Institute of Infection and Global Health, University of Liverpool, Ronald Ross Building, Liverpool, L69 7BE, UK

tsolomon@liv.ac.uk

Search strategy

We searched Scopus with the terms “meningitis”, “meningo*”, and “neurological infection” together with “aetiology”, “epidemiology”, “treatment”, “management”, “antibiotic”, “antimicrobial”, “investigation”, “therapy”, “prevention”, “vaccine*”, and “lumbar puncture” for articles published between Jan 1, 2010, and Dec 31, 2015. We also included any studies referenced within these articles if deemed relevant. In addition, any older references known to the authors were also included, as were abstracts of articles not written in English. Review articles are included to guide the reader to a more extensive reference list.

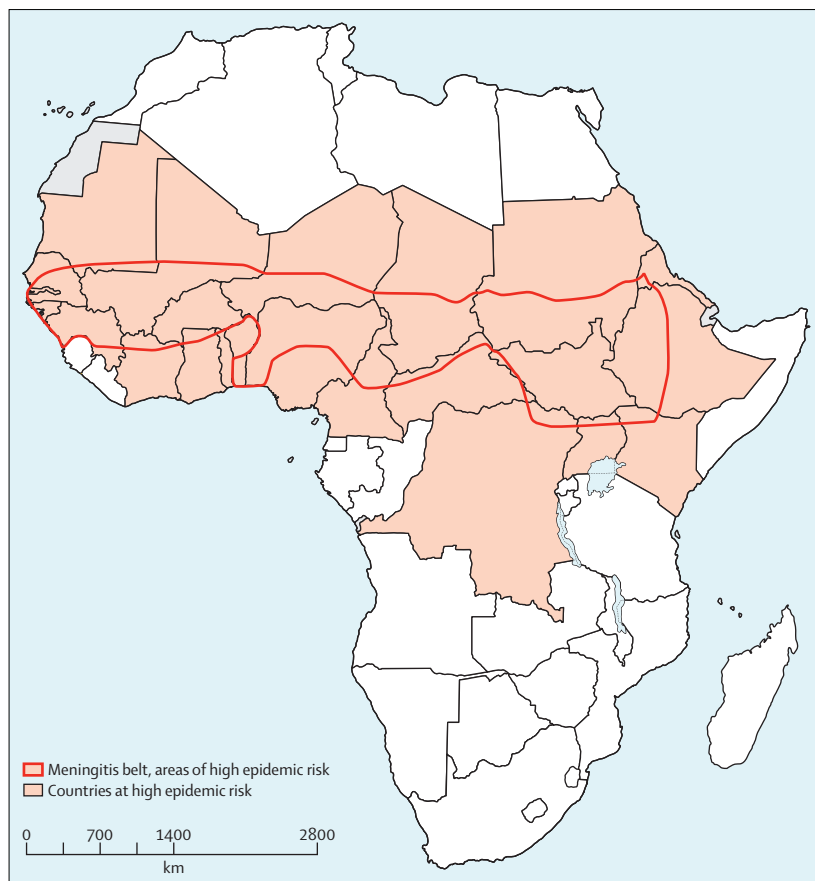


Figure 1: Areas at high risk of meningococcal meningitis, 2014

The risk differs among and within countries. Adapted with permission from WHO.

predicted a substantial reduction in disease following the introduction of PCV13, even taking serotype replacement into account.^{21,22} Observational studies²³ accord with these predictions, showing a 32% reduction in invasive pneumococcal disease following the introduction of PCV13, but a 25% increase in non-PCV13 serotypes.

Neisseria meningitidis

Meningococci are categorised into 13 serogroups; five (A, B, C, W135, and Y) are responsible for most cases of invasive disease. Serogroup B is the commonest strain across Europe, including England and Wales where it is responsible for most cases.^{24,25} Serogroup Y is predominant in the USA²⁶ and the second most common in parts of Europe.²⁷ The prevalence of serogroup W135 is increasing in the UK, which has been linked with a South American clone. Disease caused by this clone is associated with a higher mortality because they are part of the more deadly ST11 clonal complex (or cc11).²⁸ The same clonal complex is responsible for recent outbreaks of meningococcal C disease among men who have sex with men.^{29,30}

Serogroup C was previously responsible for most meningococcal disease in western Europe but incidence

has substantially declined since the introduction of the meningococcal C conjugate vaccine. In the Netherlands, incidence has declined from 4·5 cases per 100 000 people in 2001, to 0·6 cases per 100 000 people in 2012.²⁷ Similar results have been seen in other countries.^{5,14} In 2015, serogroup C disease appeared for the first time in the Sahel region of Africa.³¹ Serogroup A has been responsible for large outbreaks in the meningitis belt of Africa; however, massive reductions have occurred in recent years following widespread vaccination.^{32,33} The Meningitis Vaccine Project—a collaboration between WHO and the Programme for Applied Technology in Health—set out to vaccinate 250 million people in Africa with the new serogroup A conjugate vaccine. The project has been a massive public health triumph. In Burkina Faso, there was a risk reduction of 99·8% and similar results occurred in Niger, where serogroup A disease had virtually disappeared by 2011.^{33,34} Meningococcal A is also responsible for epidemics in parts of Asia, including India, Indonesia, Nepal, Mongolia, and Pakistan.³⁵

Other bacteria

Haemophilus influenzae type b was a significant cause of meningitis, especially in infants and young children, before the widespread use of conjugate vaccines.⁶ As with meningococcal disease, *H influenzae* type b has virtually disappeared in areas where immunisation has been implemented, but remains a problem where vaccination is not commonplace.³⁶ The incidence of invasive haemophilus disease due to non-type b strains has, however, increased. Most of these cases are due to non-typeable organisms but some due to other encapsulated forms of *H influenzae*, in particular types e and f.^{37–39}

Streptococcus suis is a major cause of meningitis in some parts of Asia, especially Thailand and Vietnam. It is a pathogen of pigs, and close contact with pigs or pork is a significant risk factor for disease. Although the case fatality rate is only 4%, some degree of hearing loss occurs in more than 50% of survivors.⁴⁰ It has also been reported from many other parts of the world.^{41–43} Other causes of meningitis include the Enterobacteriaceae, *Staphylococcus aureus*,^{1,5} and *Listeria monocytogenes* which normally occurs in patients with risk factors such as older adults, alcoholics, diabetics, patients with malignancies, and those taking immunosuppressive drugs.^{44–47}

Pathogenesis

Many aspects of the pathogenesis of bacterial meningitis have yet to be understood; however, there are four main processes: colonisation, invasion into the bloodstream, survival in the bloodstream, and entry into the subarachnoid space. The subsequent inflammation and neurological damage is caused by a combination of bacterial and host factors. Figure 2 shows the pathogenesis of *S pneumoniae* and *N meningitidis* meningitis.

Many bacteria that cause meningitis initially colonise the mucous membranes of the upper respiratory tract.

	Pathogen covered	Serotypes or serogroups covered	Type of vaccine	Protein conjugate	Vaccines available
Pneumococcal					
PCV7	<i>Streptococcus pneumoniae</i>	Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F	Conjugate 7 valent	CRM197	Prevenar
PCV10	<i>Streptococcus pneumoniae</i>	Serotypes 1*, 4*, 5*, 6B*, 7F*, 9V*, 14*, 18C†, 19F†, and 23F*	Conjugate 10 valent	Protein D*, tetanus toxoid†, diphtheria toxoid‡	Synflorix
PCV13	<i>Streptococcus pneumoniae</i>	Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	Conjugate 13 valent	CRM197	Prevenar 13
PPV23	<i>Streptococcus pneumoniae</i>	Serotypes 1, 2, 3, 4, 5, 6B, 7F 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F,	Polysaccharide, 23 valent	NA	Pneumovax II
Meningococcal					
MenACWY	<i>Neisseria meningitidis</i>	Serogroups A, C, W, Y	Conjugate, quadrivalent	CRM197§, diphtheria toxoid¶	Menveo§, Menactra¶
MPSV4	<i>Neisseria meningitidis</i>	Serogroups A, C, W, Y	Polysaccharide, quadrivalent	NA	Menomune
Hib_MenCY-TT	<i>Neisseria meningitidis</i>	Serogroups C and Y	Conjugate, bivalent	Tetanus toxoid	MenHibrix (also contains <i>Haemophilus</i> type b polysaccharide)
Men A conjugate vaccine	<i>Neisseria meningitidis</i>	Serogroup A	Conjugate, monovalent	Tetanus toxoid	MenAfriVac
Men C conjugate vaccine	<i>Neisseria meningitidis</i>	Serogroup C	Conjugate, monovalent	CRM197 or tetanus toxoid**	Meningitec , Menjugate , NeisVac-C**, Menitorix** (also contains <i>Haemophilus</i> type b polysaccharide)
Multicomponent Men B vaccine (4CMenB)	<i>Neisseria meningitidis</i>	Serogroup B	Recombinant protein based with outer membrane vesicle	NA	Bexsero
Men B bivalent vaccine	<i>Neisseria meningitidis</i>	Serogroup B	Recombinant protein based	NA	Trumenba
Haemophilus					
HiB	<i>Haemophilus influenzae</i>	Type b	Conjugate, monovalent	CRM197	Pediacel, Menitorix

CRM197 is inactive, non-toxic diphtheria toxin. Protein D is derived from non-typeable *Haemophilus influenzae*.

Table 1: Vaccines for bacterial meningitis

Colonisation involves a combination of the bacteria adhering to the cell surfaces and avoidance of the host's defence mechanisms. Many organisms have fimbriae (a fringe) or pili (hair-like appendages) that assist in their attachment to the epithelium. The main requirement for meningococcal adhesion is the type IV pili (tfp). Tfp adhere via various receptors including PAFR, β 2 adrenoceptor receptors, and CD147.^{48,49} The meningococcal outer membrane proteins including lipopolysaccharide and the opacity proteins (OpC and OpA) have also been proposed to contribute to the maintenance of adhesion.^{50,51} Three main receptors have been proposed for pneumococcal adhesion to epithelial surfaces: PAFR, laminin receptors, and PIgR.

Invasion into the bloodstream occurs either transcellularly (passing through the cells) or pericellularly (between cells).⁵² Pneumococci utilise both of these methods via receptors such as the PAFR or the pneumococcal choline binding receptor.⁵³ Meningococci are transported across the epithelial cells in phagocytic vacuoles.⁵⁴ Survival in the bloodstream requires evasion of the immune system. Meningococci utilise fHbp, a lipoprotein responsible for dysregulation of the complement pathway and PorA, an outer membrane protein, to evade complement.^{55,56}

Most cases of meningitis probably occur following bacteraemia but the high incidence of pneumococcal

meningitis in patients with sinusitis and otitis media suggest that direct spread to the CNS might also occur. This possibility is supported by mouse models showing pneumococcal meningitis after respiratory infection without bloodstream involvement.⁵⁷ Direct entry from the nose through dural defects is also possible.

Because of a lack of host defences in the subarachnoid space, bacteria multiply there relatively unhindered. Bacterial components are recognised by pattern recognition receptors, present on microglia and other brain cells. A cascade of events is then triggered that ultimately leads to the release of pro-inflammatory mediators such as TNF α , interleukin 6, and interleukin 1 β . Many of these molecules are released in greater quantity in pneumococcal meningitis than in meningitis caused by other organisms and could account for the worse prognosis associated with pneumococcal meningitis.⁵⁸ Following the release of the cytokines, granulocytes cross the blood-brain barrier and it becomes more permeable. Bacterial lysis occurs in response to antibiotics or, in the case of pneumococci, when the bacteria reach the stationary growth phase (autolysis). Lysis leads to the release of pro-inflammatory agents, such as lipopolysaccharide, lipoteichoic acid, and peptidoglycans, from the cell wall of the bacterium and augments the inflammatory process.⁵⁹

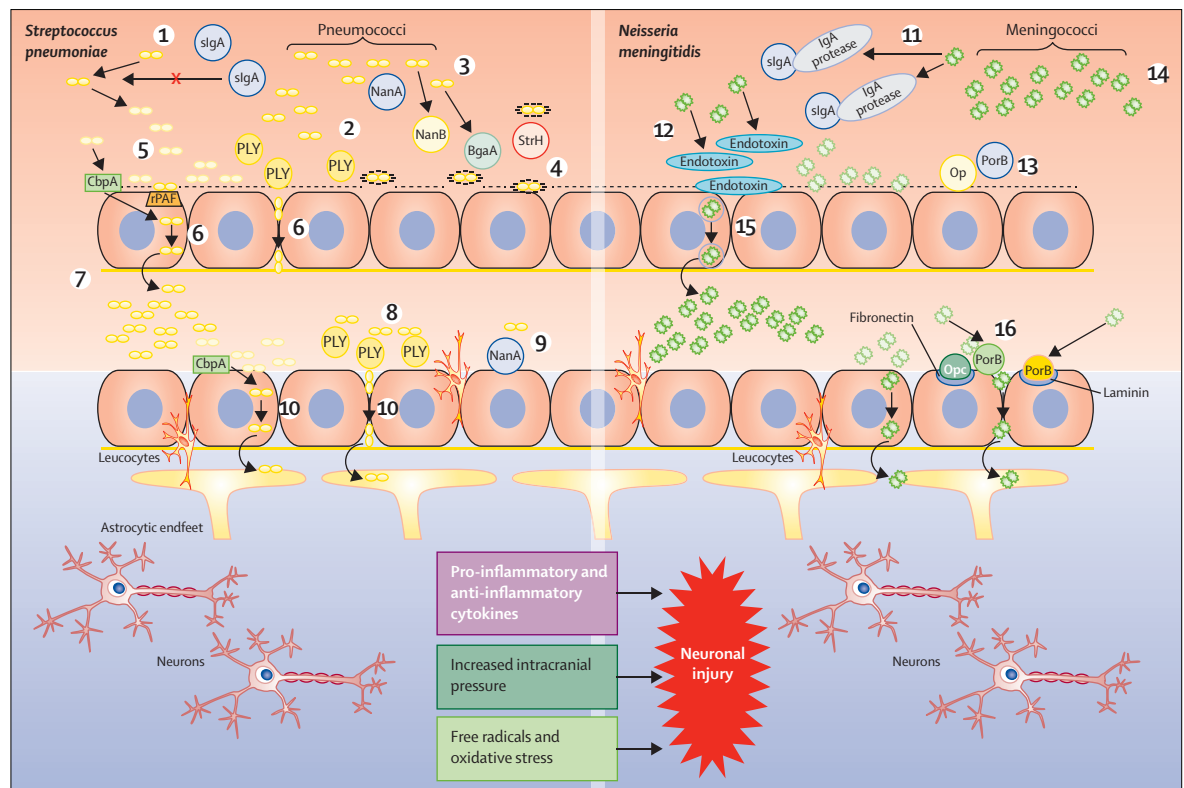


Figure 2: Mechanistic pathways in the pathogenesis of bacterial meningitis

Colonisation by pneumococcus is achieved by various stepwise mechanisms. The opaque capsule of the bacteria prevents IgA to remove the bacteria from the nasopharynx (1). Release of the PLY toxin from lysed bacteria reduces ciliary contractility of the upper airway (2), whereas deglycosylation of the mucus reduces further cilia activity (3). The negative charge surrounding the capsule, opposes the negative charge of the sialic acid in mucus (4). Additionally, the phase variation of the capsule from opaque to transparent enables adhesion molecules to bind to the epithelium (5). Invasion of pneumococci into the bloodstream is achieved by transcytotic or paracellular mechanisms (6) and degradation of the cells' extracellular matrix (7). The pneumococci then enter the nervous system by following similar mechanistic pathways to the upper airway (8, 9, 10). For meningococcal meningitis, colonisation is achieved by inhibiting IgA function similarly to the pneumococci (11). Secretion of endotoxins (12) and capsular saccharides (13) as well as the use of meningococcal pili (14), enables the bacteria to bind on the epithelial cells. Invasion into the bloodstream is achieved by the encapsulation of bacteria by phagocytes (15). The bacteria enter the bloodstream and further invade the nervous system transcellularly or paracellularly either binding to fibronectin or laminin (16). For both pneumococcal and meningococcal meningitis, the blood-brain barrier breaks down and cytokines and white blood cells cross into the brain, initiating further inflammatory responses. Intracranial pressure is increased and lysis of the bacteria promotes the creation of free radicals, which can lead to oxidative stress and neuronal damage.

Neutrophils have been implicated in much of the neurological damage that occurs in meningitis and MRP-14, a protein expressed in myeloid cells, has been found in the cerebrospinal fluid of patients with pneumococcal meningitis; inhibition of MRP-14 reduced sequelae in a mouse model.⁶⁰ Matrix metalloproteinases (MMPs) are released by white blood cells in the CSF. They are present very early in infection and aid the release and activation of pro-inflammatory cytokines, the degradation of extracellular matrix components, and the recruitment of further leucocytes into the subarachnoid space. As with other inflammatory mediators, the levels of MMP-9 are especially high in pneumococcal meningitis compared with meningitis caused by other organisms.⁵⁸

Genetic predisposition

Several studies have suggested a genetic predisposition to bacterial meningitis, with most related to deficiencies

that affect the complement system. In particular, C2 deficiency has been reported in 58% of patients with pneumococcal meningitis, factor D deficiency predisposes to meningococcal disease, and susceptibility to meningococcal serogroups W135 and Y arises in people with properdin deficiency.⁶¹ Case-control studies⁶¹ showed that polymorphisms in mannose-binding lectin and *cfh* are associated with susceptibility to pneumococcal and meningococcal disease, respectively. Roughly a fifth of patients with meningococcal disease were defined as having meningitis. Because of variations in definitions, no analysis could be done excluding patients who did not have meningitis. Genome wide association studies^{62,63} have confirmed that a polymorphism in *cfh* predisposes to meningococcal disease, just over a third of patients in these studies had meningitis, and a polymorphism in the C3 gene predisposed to pneumococcal meningitis.

	Appearance	Opening pressure (cm CSF)	White blood cell concentration (cells per μ L)	Predominant cell type	CSF protein (g/L)	CSF glucose (mmol)	CSF:serum glucose ratio
Normal	Clear	10–20	<5	NA	<0.4	2.6–4.5	>0.66
Bacterial	Turbid, cloudy, purulent	Raised	Raised (normally >100)	Neutrophils	Raised (normally >1.0)	Low	Very low
Viral	Clear	Normal or mildly raised	Raised (normally <1000)	Lymphocytes	Mildly raised (normally 0.5–1)	Normal or slightly low	Normal or slightly low
Tuberculous	Clear, cloudy	Raised	Raised (normally <500)	Lymphocytes	Greatly raised	Low	Very low

Adapted from Solomon et al.⁶⁵ A traumatic lumbar puncture will affect the results and a correction factor such as the following should be applied: adjusted white blood cells in CSF=measured white blood cells in CSF–[(white blood cells in blood \times red blood cells in CSF) / red blood cells in blood \times 1 000 000]. Local laboratory ranges for biochemical tests should be consulted and might vary from those here. CSF=cerebrospinal fluid.

Table 2: Classic features of cerebrospinal fluid for the different causes of meningitis

Diagnosis

Diagnosing bacterial meningitis clinically can be difficult because many illnesses present with similar symptoms. The classical triad of neck stiffness, fever, and altered consciousness occurs in less than 50% of patients with acute bacterial meningitis.⁸ However, any two of headache, fever, neck stiffness, and altered consciousness are much more common, in up to 95% of patients.⁸ Kernig's and Brudzinski's signs have been used in the clinical assessment of meningitis for many years, but their usefulness is doubtful. They have been reported to have high specificity (up to 95%), although this is dependent on the clinician, but the sensitivity can be as low as 5%.⁶⁴ They should not be relied on to exclude, or establish, a diagnosis of bacterial meningitis. Differential diagnoses include viral meningitis and other forms of infective meningitis, non-infectious causes of meningitis such as autoimmune conditions, medications such as trimethoprim and non-steroidal anti-inflammatory drugs, and malignancy, as well as non-meningitic illnesses such as sub-arachnoid haemorrhage, migraine, and other simple viral illnesses.

The gold standard for diagnosing meningitis is examination of the cerebrospinal fluid (table 2). Measuring the opening pressure at the time of lumbar puncture is useful and is often high in patients with bacterial meningitis. A high white blood cell count in the cerebrospinal fluid can indicate inflammation of the meninges, although some patients might have bacteria in their cerebrospinal fluid without an elevated white blood cell count. These patients have a poor prognosis.

Cerebrospinal fluid protein and glucose should also be measured. Patients with bacterial meningitis typically have high protein and low glucose. Cerebrospinal fluid glucose is influenced by the serum glucose concentration and, therefore, a concurrent serum sample must also be taken. Cerebrospinal fluid lactate may have advantages over glucose in that it is unaffected by the serum concentration. Cerebrospinal fluid lactate, if taken before antibiotic treatment, has a sensitivity of 0.93 (95% CI 0.89–0.96) and specificity of 0.96 (0.93–0.98) in differentiating bacterial from viral meningitis.⁶⁶ Serum

and cerebrospinal fluid procalcitonin concentrations have also been suggested as useful tests to indicate a likely bacterial cause but well-designed diagnostic accuracy studies, including cost-effectiveness analyses, are needed before recommending the routine use of procalcitonin for diagnosis of bacterial meningitis.

Gram stain and culture of the cerebrospinal fluid enable both the identification of the causative pathogen and assessment of antimicrobial susceptibilities. If the lumbar puncture is delayed until after antibiotics have been given, the likelihood of identifying an organism might be reduced by up to 44%.^{48,67} Molecular methods are, therefore, becoming increasingly important for diagnosis. The most common of these is PCR, which can detect organisms in blood or cerebrospinal fluid for several days after antibiotics have been given.^{49,68} It has high sensitivity (87–100%) and specificity (98–100%).^{69–72} Dried spot cerebrospinal fluid PCR tests, which could be useful in the absence of a laboratory, have shown a 90% sensitivity in diagnosing bacterial meningitis caused by *S pneumoniae*, *S suis*, and *N meningitidis*.⁷³ In addition to cerebrospinal fluid analysis, blood cultures might identify the cause and should be taken before antibiotics are given.

There has been interest in the ability to detect multiple pathogens with one platform, such as multiplex PCR, 16S PCR, MALDI-TOF, and whole genome sequencing.^{74,75} The 16S rRNA gene is present in almost all bacteria; one meta-analysis⁷⁶ showed 16S rRNA PCR to be both sensitive and specific for the diagnosis of bacterial meningitis compared with standard culture (pooled sensitivity of 92% and specificity of 94%). The commonest method for species identification after 16S PCR was sequencing. MALDI-TOF is now commonplace in many clinical laboratories. It utilises the protein mass of the organism to identify the bacteria. This has revolutionised clinical microbiology by reducing the time to identification of an organism; it normally requires a cultured organism but there are reports of success direct from cerebrospinal fluid.⁷⁷ Whole genome sequencing has been used to investigate outbreaks, but as it becomes faster and cheaper, it may be incorporated into routine surveillance and diagnosis.^{78,79}

	Preferred choice		Alternative if anaphylaxis to β lactams	
	Standard treatment	Alternative in areas of high prevalence of penicillin resistance*	Standard therapy	Alternative in areas of high prevalence of penicillin resistance*
Adults <60 years of age†	Cefotaxime 2 g intravenously every 4–6 h or ceftriaxone 2 g intravenously every 12 h	Cefotaxime 2 g intravenously every 4–6 h or ceftriaxone 2 g intravenously every 12 h; plus vancomycin 15–20 mg/kg intravenously every 8–12 h‡ with or without rifampicin 600 mg intravenous or orally every 24 h§	Chloramphenicol 25 mg/kg intravenously every 6 h	Vancomycin 15–20 mg/kg intravenously every 8–12 h‡ plus moxifloxacin 400 mg intravenously every 24 h¶
Adults ≥60 years of age	As above; plus amoxicillin or ampicillin 2 g intravenously every 4 h	As above; plus amoxicillin or ampicillin 2 g intravenously every 4 h	As above; plus co-trimoxazole 5 mg/kg (of the trimethoprim component) intravenously every 6–12 h	As above; plus co-trimoxazole 5 mg/kg (of the trimethoprim component) intravenously every 6–12 h

Doses are given as a guide only and should not be relied on for prescribing purposes. They also reflect the doses suitable for patients with normal renal and hepatic function. *Eg, USA, southern and eastern Europe, Asia. †Amoxicillin (or co-trimoxazole if allergic to penicillin) should be added in patients younger than 60 if listerial infection is suspected—eg, in immunocompromised patients. ‡Maintain serum trough concentrations of 15–20 mg/mL. §Some authorities would recommend either vancomycin or rifampicin. ¶No clinical data available on optimum dosage in patients with bacterial meningitis.

Table 3: Suggested empirical antibiotic choices for patients with bacterial meningitis

Loop-mediated isothermal amplification is another method of DNA amplification and detection. The method is quick, with results in less than 2 h, and a positive result can be seen with the naked eye. This technique has shown good sensitivity for detection of *N meningitidis*, *S pneumoniae*, *H influenzae*, and *Mycobacterium tuberculosis*.^{80–83} It has also been assessed as a bedside test in the UK, for which it had a positive predictive value of 100% and a negative predictive value of 97%.⁸⁴ The speed and ease of diagnosis makes this a very attractive diagnostic tool, especially in resource poor settings.

The use of neuroimaging before lumbar puncture has generated considerable debate with some recommending that cerebral imaging is done before lumbar puncture for all patients. However, this approach has been associated with delays in antibiotic administration, reduced likelihood of identifying a pathogen, and an increase in mortality.^{48,52,85,86} The reason for neuroimaging is to detect cerebral herniation syndromes, or shift of brain compartments. If these are present and a lumbar puncture is done, there is the theoretical concern that a reduction in pressure caused by the lumbar puncture can precipitate a further brain shift, which could lead to fatal herniation. Neuroimaging should therefore be done for patients who have clinical signs that might suggest brain shift and, if shift of brain compartments or herniation is found, lumbar puncture should be delayed. Indications that brain shift might be present include focal neurological signs and reduced level of consciousness. The exact level of consciousness at which a lumbar puncture is safe is debated and different authorities recommend different cutoff points ranging between 8 and 13 on the Glasgow coma scale.^{87–89}

No study has identified features associated with an increased risk of herniation after lumbar puncture. One study showed that certain features (age >60 years, immunocompromised, history of neurological disease, recent seizure, and some abnormal neurological examination findings) were associated with abnormalities on imaging, but the risk of herniation or brain shift was not assessed.⁸⁶ A retrospective study⁹⁰ showed that

removing impaired mental status as a contraindication for lumbar puncture was associated with significantly earlier treatment and a favourable outcome; however, there are several limitations to this study and cause and effect cannot be attributed. Every patient with suspected bacterial meningitis should be carefully assessed to ascertain whether they have signs or symptoms consistent with brain shift. If they do not, lumbar puncture should be done as soon as possible without prior neuroimaging (appendix).

Treatment

Antibiotics should be given as soon as possible to patients with suspected bacterial meningitis, ideally after both blood and cerebrospinal fluid have been obtained for culture. Early antibiotic treatment is associated with a lower mortality.⁸⁵ If sampling is delayed, the priority is for treatment to be given. Many antibiotic regimens are based on data from animal models or clinical experience rather than randomised trials. The choice of antibiotic depends on the likely pathogen, local patterns of antibiotic resistance, and the cerebrospinal fluid penetration of the drug (table 3). Penicillin and other β -lactams are effective against the commonest pathogens and the cerebrospinal fluid concentration (even with uninflamed meninges) tends to be close to the minimum inhibitory concentrations for moderately susceptible bacteria.⁹¹ The worldwide emergence of antimicrobial resistance, especially against *S pneumoniae*, affects the choice of empirical treatment in many countries. This is especially important in the poorer regions of the world, where newer antibiotics might not be available or affordable.

Penicillin-resistant pneumococci have been reported from all parts of the world⁹² and have been associated with an increase in mortality.⁹³ Vancomycin is widely recommended when penicillin-resistant pneumococci might be present, but because it crosses the blood–brain barrier poorly it should be used in conjunction with another antimicrobial, often a cephalosporin.

Fluoroquinolones might be good alternatives in the era of penicillin-resistant pneumococci. Experimental

See Online for appendix

mouse models have shown moxifloxacin to be equivalent to cephalosporins for treatment of pneumococcal meningitis and cerebritis.⁹⁴ Caution should be exercised in using fluoroquinolones as single drugs because organisms might rapidly develop resistance and clinical data are lacking. There are several case reports and case series showing the efficacy of other antibiotics in meningitis, such as ceftaroline,⁹⁵ linezolid,^{96,97} daptomycin,^{98–100} and doripenem.¹⁰¹ Without evidence from comparative trials, these drugs should be used with caution and only when other better tested drugs cannot be used either because of resistance, patient intolerance, or allergy.

Efforts should be made to identify local patterns of antibiotic resistance to determine the best empirical treatment for each geographical area. In the UK, where penicillin resistance is rare, third-generation cephalosporins (cefotaxime or ceftriaxone) remain the empirical choice. However, many parts of the world have penicillin-resistant pneumococci (minimum inhibitory concentration ≥ 0.12 $\mu\text{g/mL}$). It occurs in roughly 25% of cases in the USA and parts of Europe (eg, Spain, Croatia, Romania), and more than 50% in Asia; 100% of isolates have been reported to be penicillin resistant in Vietnam and Thailand but numbers were small ($n=6$ and $n=1$, respectively).^{102–104} In these areas, vancomycin (with or without rifampicin) should be given in addition to a third-generation cephalosporin (table 3).¹⁰⁵

Antibiotic resistance in meningococci is rare,²⁷ although decreased susceptibility to penicillin has been associated with some serogroups, especially C and W135.^{106–109}

There is limited trial evidence to guide how long to treat adults with bacterial meningitis. Using shorter courses of antibiotics can reduce hospital stay and costs and might also reduce the risk of adverse events such as nosocomial infections. Studies in children have shown that shorter courses are safe and effective.^{110,111} A meta-analysis¹¹² of all causes of bacterial meningitis in children showed a short course (4–7 days) to be as efficacious as a long course (7–14 days) of antibiotics; we are unaware of any studies in adults. 3 days of intravenous benzylpenicillin has been shown to be sufficient for adults with meningococcal disease;¹¹³ there was no control group in this study, but the mortality of 9% is in keeping with other studies.^{8,25,114} During meningococcal epidemics, a single dose of ceftriaxone or chloramphenicol is effective.¹¹⁰

Although there are no randomised trials, current guidance in many rich nations is to give short courses of antibiotics for meningococcal disease (5–7 days), and a slightly longer course for pneumococcal meningitis (10–14 days).^{115,116} *Listeria* meningitis should be treated for a minimum of 21 days.

Even in the presence of a susceptible organism and appropriate antibiotics, mortality in bacterial meningitis is high, around 10–30% in high-income countries,^{4,8,114,117–120} and nearer 50% in many poorer nations.^{121–123} The high

number of deaths, despite apparently appropriate treatment, is thought to be due to inflammatory processes. Therefore, efforts have focused on identifying useful adjunctive treatments that might reduce inflammation and brain oedema.

Following several studies of children,¹²⁴ a large multicentre European randomised controlled trial in adults showed a significant reduction of both an unfavourable outcome and death in patients who were treated with dexamethasone compared with placebo (relative risk 0.59 for unfavourable outcome and 0.48 for death), most striking for the subgroup of patients with pneumococcal meningitis.¹²⁵ Subsequent studies of adults in Malawi and Vietnam did not reproduce the European findings,^{123,126} although there was a better outcome (significant reduction in the risk of death at 1 month and risk for death or disability at 6 months) for patients in Vietnam with confirmed bacterial meningitis. A meta-analysis of individual patient data ($n=2029$) suggested the differences were not due to the high rates of HIV and tuberculosis in these countries.¹²⁷ This meta-analysis concluded that there were no subgroups that might benefit from adjunctive dexamethasone, although post-hoc analyses did suggest that there might be some benefit in HIV-negative adults and a lower rate of hearing loss among all survivors.

Another meta-analysis of 25 studies,¹²⁴ in both adults and children, showed a small reduction in hearing loss in adults treated with corticosteroids compared with placebo (16% vs 22%; risk ratio 0.74, 95% CI 0.56–0.98) but no difference in mortality. A subgroup analysis showed a slight decline in mortality in all patients with pneumococcal meningitis (risk ratio 0.84, 95% CI 0.72–0.98) with no effect on *H influenzae* or meningococcal meningitis (although numbers in these groups were very small). This benefit did not remain when a random-effects model was used (which may have been more appropriate given the heterogeneity of the studies: I^2 47%).¹²⁴

Both these meta-analyses compared very diverse studies and populations including children and adults, high and low socioeconomic status, and differences in comorbidities. This variation is reflected in the heterogeneity of the analyses and possibly accounts for the conflicting conclusions. However, there should be a balance between the risks and potential benefits of corticosteroid use. Overall, corticosteroids seem to offer a small benefit in adults with regard to reducing hearing loss and might slightly lower mortality in pneumococcal meningitis. In most studies, there is no increase in side-effects when corticosteroids were given in comparison to placebo. Therefore, steroids are recommended for all adults with suspected bacterial meningitis in resource-rich countries. Although the meta-analyses did not show a difference between countries of high and low income, there was considerable heterogeneity and in lower income countries the benefits are probably less

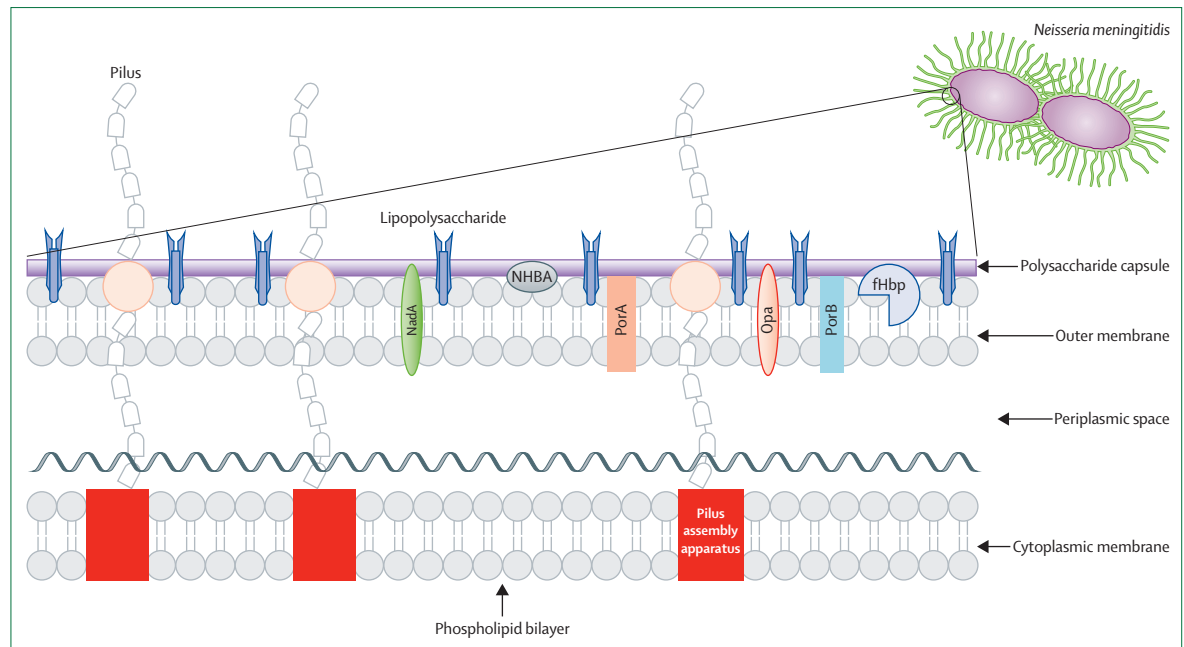


Figure 3: Major outer membrane components of *Neisseria meningitidis* and vaccine targets

The polysaccharide capsule determines the serogroup whereas the outer membrane proteins porA and porB determine the serosubtype and serotype, respectively.

pronounced; therefore, corticosteroids are not recommended in this group.

The dose of corticosteroids differs between trials, but the one that was used in the large European trial is 10 mg of dexamethasone given four times a day.¹²⁵ The Cochrane review¹²⁴ recommends administration with or just before the first antimicrobial dose.¹²⁴ Subgroup analyses in both meta-analyses showed no statistical differences in terms of mortality when corticosteroids were given before or with antibiotics compared with when they were given afterwards.^{124,127} There were differences when hearing loss was the outcome of interest and the effect size was bigger in the group who received corticosteroids after antibiotics compared with the group who received corticosteroids before or concurrently (risk ratio 0·62, 95% CI 0·43–0·89 vs 0·8, 0·7–0·92).¹²⁴

Glycerol and hypothermia have been trialled as potential adjunctive therapies in bacterial meningitis. Theoretically, osmotic substances such as glycerol can draw extravascular fluid from the brain into the vascular space and reduce intracranial pressure. One clinical study in adults,¹²¹ done in a resource-limited setting with a high HIV prevalence, showed no benefit. Induced hypothermia is used as a treatment for cerebral hypoxaemia following cardiac arrest and animal models have shown it to reduce intracranial hypertension in meningitis. Observational clinical studies^{128,129} also suggested it might be beneficial. However, a randomised controlled trial¹³⁰ was stopped early because of an increased risk of death in patients in the intervention group. It is unlikely that hypothermia or glycerol will be widely implemented without adaptation and further controlled trials.

Prognosis and sequelae

Features associated with a poor prognosis include older age, reduced conscious level, tachycardia, a cerebrospinal fluid leucocyte count of less than 1000×10^9 cells per mL, and reduced platelet count.⁸ Prognosis can be improved by instigating both antibiotic and steroid treatment early.³ Sequelae are more common in pneumococcal meningitis than meningococcal meningitis. Hearing loss is one of the most common problems after meningitis, particularly pneumococcal meningitis, and a prompt hearing assessment with cochlear implants can be beneficial for patients. Other sequelae include limb loss, especially if meningococcal sepsis occurs, subdural empyema, hydrocephalus, and seizures. Other less life-threatening sequelae include neurocognitive dysfunction such as sleep disorders.

The future

Many of the pneumococcal vaccines in development are protein based (rather than being based on the capsular polysaccharide), to be given either in addition or as an alternative to conjugate vaccines. This approach could provide pan-serotype protection and eliminate the problem of serotype replacement. Several early phase studies have been done, one of which (combining pneumolysin toxoid and histidine triad protein D, a pneumococcal surface protein thought to be involved in complement inhibition) has provided good evidence of immunogenicity with an acceptable safety profile in both younger and older adults.^{131–133}

The search for a widely effective vaccine against meningococcal serogroup B has been difficult because of

the poorly immunogenic capsule. Vaccines were developed that targeted subcapsular proteins (figure 3) and were used with some success in epidemics in Norway, Cuba, Brazil, New Zealand, and France.^{134–136} However, they were poorly immunogenic in young children and strain specific, and so could not be rolled out on a larger scale. Using a novel genome sequencing method, a multicomponent serogroup B meningococcal vaccine has been produced. It contains four immunogenic components: three proteins (NadA, which is involved in the adhesion of *Neisseria* to the nasal epithelium; NHBA, thought to be involved in serum resistance; and fHbp) in combination with outer membrane vesicles from the New Zealand vaccine strain. The vaccine is immunogenic in young infants^{137,138} and older children.¹³⁹ It might also reduce carriage of other meningococcal serogroups (because some of the subcapsular antigens in the vaccine are also present in non-B serogroups),¹⁴⁰ indicating that it could affect transmission once fully implemented and have a significant effect on disease in adults as well as children. The vaccine has been estimated to provide coverage against 88% of circulating serogroup B strains in England and Wales,¹⁴¹ and was permitted for investigational use in the USA in late 2013 and early 2014 in two outbreaks. In September, 2015, the UK Department of Health incorporated it into their childhood immunisation schedule. The US Food and Drug Administration have also approved another serogroup B vaccine for adolescents and young adults. This vaccine is a bivalent vaccine that utilises two families of fHbp.

New treatments are needed. Research is focused on adjunctive therapy targeting the host inflammatory response. Some areas of interest include MMP inhibitors and MRP-14 inhibitors such as paquinimod, which has anti-inflammatory effects without affecting bacterial killing.⁶⁰ Inhibitors of complement and other neurotoxic mediators are also being investigated as well as compounds that can modulate the leucocyte response (eg, G-CSF).¹⁴²

Finally, surveillance around the world remains important. The global epidemiology of bacterial meningitis is continually changing, especially with the introduction of new vaccines, and surveillance is needed to determine the breadth of coverage, monitor for serotype replacement, and follow the emergence of new meningococcal serogroups. Robust epidemiological studies should document clearly the causative agents in low-resource settings, especially Asia, to determine what vaccination strategies are necessary. Surveillance for antimicrobial resistance is also of utmost importance. Epidemiological research into risk factors for disease in adults and preventive strategies is also needed.

Effective control of bacterial meningitis is still some way off. Because the disease is both rare and deadly, it requires the vigilance of the clinician to identify and treat it in a timely manner, and the continued support of research partners to develop new vaccines and treatments.

Contributors

FM and TS decided on the scope and plan for the Seminar. FM searched the published work and drafted the first version of the Seminar. All authors then contributed to further drafts and approved the final submitted version. SP gave specific input to the pathogenesis section and designed figures 2 and 3.

Declaration of interests

We declare no competing interests.

Acknowledgments

FM is a National Institute for Health Research (NIHR) doctoral research fellow and TS is an NIHR senior investigator. Both receive support from the NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health, or Public Health England. This work was conducted independently of influence from the NIHR.

References

- Okike IO, Ribeiro S, Ramsay M, Heath PT, Sharland M, Ladhani SN. Trends in bacterial, mycobacterial and fungal meningitis in England and Wales 2004–11: an observational study. *Lancet Infect Dis* 2014; **14**: 301–07.
- Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009; **27S**: B51–63.
- Bijlsma MW, Brouwer M, Soemirien Kasanmoentalib E, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 2016; **16**: 339–47.
- Pórdardóttir A, Erlendsdóttir H, Sigurdardóttir B, et al. Bacterial meningitis in adults in Iceland, 1995–2010. *Scand J Infect Dis* 2014; **46**: 354–60.
- Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. *Lancet Infect Dis* 2014; **14**: 813–19.
- Martin NG, Sadarangani M, Pollard A, Goldacre MJ. Hospital admission rates for meningitis and septicaemia caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* in children in England over five decades: a population-based observational study. *Lancet Infect Dis* 2014; **14**: 397–405.
- GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**: 117–71.
- van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; **351**: 1849–59.
- Domingo P, Pomar V, Benito N, et al. The changing pattern of bacterial meningitis in adult patients at a large tertiary university hospital in Barcelona, Spain (1982–2010). *J Infect* 2013; **66**: 147–54.
- Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 2015; **372**: 1114–25.
- Fletcher MA, Balmer P, Bonnet E, Dartois N. PCVs in individuals at increased risk of pneumococcal disease: a literature review. *Expert Rev Vaccines* 2015; **14**: 975–1030.
- Sadarangani M, Scheifele DW, Halperin SA, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. *Clin Infect Dis* 2015; **60**: e27–35.
- Bijlsma MW, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. A decade of herd protection after introduction of meningococcal serogroup C conjugate vaccination. *Clin Infect Dis* 2014; **59**: 1216–21.
- Sadarangani M, Scheifele DW, Halperin SA, et al. The impact of the meningococcal serogroup C conjugate vaccine in Canada between 2002 and 2012. *Clin Infect Dis* 2014; **59**: 1208–15.
- Harboe ZB, Dalby T, Weinberger DM, et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin Infect Dis* 2014; **59**: 1066–73.
- Parra EL, De La Hoz F, Diaz PL, et al. Changes in *Streptococcus pneumoniae* serotype distribution in invasive disease and nasopharyngeal carriage after the heptavalent pneumococcal conjugate vaccine introduction in Bogota, Colombia. *Vaccine* 2013; **31**: 4033–38.

- 17 Chiba N, Morozumi M, Shouji M, et al. Rapid decrease of 7-valent conjugate vaccine coverage for invasive pneumococcal diseases in pediatric patients in Japan. *Microb Drug Resist* 2013; **19**: 308–15.
- 18 Shibl AM, Memish ZA, Al-Kattan KM, Shibl AM, Memish ZA, Al-Kattan KM. Antibiotic resistance and serotype distribution of invasive pneumococcal diseases before and after introduction of pneumococcal conjugate vaccine in the Kingdom of Saudi Arabia (KSA). *Vaccine* 2012; **30**: G32–36.
- 19 Ho P, Chiu SS, Ang I, Lau Y. Serotypes and antimicrobial susceptibilities of invasive *Streptococcus pneumoniae* before and after introduction of 7-valent pneumococcal conjugate vaccine, Hong Kong, (1995–2009). *Vaccine* 2011; **29**: 3270–75.
- 20 Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. *PLoS Med* 2013; **10**: e1001517.
- 21 Choi YH, Jit M, Flashce S, Gay N, Miller E. Mathematical modelling long-term effects of replacing Pevnar7 with Pevnar13 on invasive pneumococcal diseases in England and Wales. *PLoS One* 2012; **7**: e39927.
- 22 Link-Gelles R, Taylor T, Moore MR, Active Bacterial Core Surveillance Team. Forecasting invasive pneumococcal disease trends after the introduction of 13-valent pneumococcal conjugate vaccine in the United States, 2010–2020. *Vaccine* 2013; **31**: 2572–77.
- 23 Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MPE, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis* 2015; **15**: 535–43.
- 24 Public Health England. Meningococcal disease: laboratory confirmed cases in England and Wales. 2014. <https://www.gov.uk/government/publications/meningococcal-disease-laboratory-confirmed-cases-in-england-and-wales> (accessed Sept 29, 2014).
- 25 Ladhani SN, Flood JS, Ramsay ME, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. *Vaccine* 2012; **30**: 3710–16.
- 26 Cohn AC, MacNeil JR, Harrison LH, et al. Changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998–2007: implications for prevention of meningococcal disease. *Clin Infect Dis* 2010; **50**: 184–91.
- 27 Bijlsma MW, Bekker V, Brouwer M, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960–2012: an analysis of national surveillance data. *Lancet Infect Dis* 2014; **14**: 805–12.
- 28 Lucidarme J, Hill DMC, Bratcher HB, et al. Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. *J Infect* 2015; **71**: 544–52.
- 29 Aubert L, Taha MK, Boo N, et al. Serogroup C invasive meningococcal disease among men who have sex with men and in gay-oriented social venues in the Paris region: July 2013 to December 2014. *Euro Surveill* 2015; **20**: 21016.
- 30 Marcus U, Vogel U, Schubert A, et al. A cluster of invasive meningococcal disease in young men who have sex with men in Berlin, October 2012 to May 2013. *Euro Surveill* 2013; **18**: 20523.
- 31 WHO. Rapidly growing outbreak of meningococcal disease in Niger. 2015. <http://www.who.int/mediacentre/news/situation-assessments/meningitis-niger/en/> (accessed June 3, 2015).
- 32 Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014; **383**: 40–47.
- 33 Collard JM, Issaka B, Zaneidou M, et al. Epidemiological changes in meningococcal meningitis in Niger from 2008 to 2011 and the impact of vaccination. *BMC Infect Dis* 2013; **13**: 576.
- 34 Novak RT, Kambou JL, Diomandé FVK, et al. Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data. *Lancet Infect Dis* 2012; **12**: 757–64.
- 35 Vyse A, Wolter JM, Chen J, Ng T, Soriano-Gabarro M. Meningococcal disease in Asia: an under-recognized public health burden. *Epidemiol Infect* 2011; **139**: 967–85.
- 36 Ramachandran P, Fitzwater SP, Aneja S, et al. Prospective multi-centre sentinel surveillance for *Haemophilus influenzae* type b & other bacterial meningitis in Indian children. *Indian J Med Res* 2013; **137**: 712–20.
- 37 Wan Sai Cheong J, Smith H, Heney C, et al. Trends in the epidemiology of invasive *Haemophilus influenzae* disease in Queensland, Australia from 2000 to 2013: what is the impact of an increase in invasive non-typable *H. influenzae* (NTHi)? *Epidemiol Infect* 2015; **143**: 2993–3000.
- 38 Rubach MP, Bender JM, Mottice S, et al. Increasing incidence of invasive *Haemophilus influenzae* disease in adults, Utah, USA. *Emerg Infect Dis* 2011; **17**: 1645–50.
- 39 Ladhani S, Slack MPE, Heath PT, et al. Invasive *Haemophilus influenzae* disease, Europe, 1996–2006. *Emerg Infect Dis* 2010; **16**: 455–63.
- 40 Vu Thi Lan H, Ngo H, Nguyen Tien H, et al. Epidemiology, clinical manifestations, and outcomes of *Streptococcus suis* infection in humans. *Emerg Infect Dis* 2014; **20**: 1105–14.
- 41 Fowler HN, Brown P, Rovira A, et al. *Streptococcus suis* meningitis in swine worked, Minnesota, USA. *Emerg Infect Dis* 2013; **19**: 330–31.
- 42 Gomez-Zorrilla S, Ardanuy C, Lora-Tamayo J, et al. *Streptococcus suis* infection and malignancy in man, Spain. *Emerg Infect Dis* 2014; **20**: 1067–68.
- 43 Demar M, Belzunce C, Simmonnet C, et al. *Streptococcus suis* meningitis and bacteremia in man, French Guiana. *Emerg Infect Dis* 2013; **19**: 1454–56.
- 44 Gerner-Smidt P, Ethelberg S, Schiellerup P, et al. Invasive listeriosis in Denmark 1994–2003: a review of 299 cases with special emphasis on risk factors for mortality. *Clin Microbiol Infect* 2005; **11**: 618–24.
- 45 Koopmans MM, Brouwer M, Bijlsma MW, et al. *Listeria monocytogenes* sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study. *Clin Infect Dis* 2013; **57**: 247–53.
- 46 Roed C, Neess Engsig F, Omland LH, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with *Listeria monocytogenes* meningitis: a Danish nationwide cohort study. *J Infect* 2012; **64**: 34–40.
- 47 Gillespie IA, McLauchlin J, Little CL, et al. Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007. *J Clin Microbiol* 2009; **47**: 3301–07.
- 48 Michael B, Menezes B, Cuniffe J, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J* 2010; **27**: 433–38.
- 49 Bryant PA, Li HY, Zaia A, et al. Prospective study of a real-time PCR that is highly sensitive, specific, and clinically useful for diagnosis of meningococcal disease in children. *J Clin Microbiol* 2004; **42**: 2919–25.
- 50 Trivedi K, Tang CM, Exley RM. Mechanisms of meningococcal colonisation. *Trends Microbiol* 2011; **19**: 456–63.
- 51 Coureuil M, Bourdoulous S, Marullo S, Nassif X. Invasive meningococcal disease: a disease of the endothelial cells. *Trends Mol Med* 2014; **20**: 571–78.
- 52 Aronin SI, Peduzzi P, Quagliarello VJ. Community acquired bacterial meningitis risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; **129**: 862–69.
- 53 Cundell DR, Gerard NP, Gerard C, Idanpaan-Helkkila I, Tuomanen E. *Streptococcus pneumoniae* anchor to activated human cells by the receptor for platelet-activating factor. *Nature* 1995; **377**: 435–38.
- 54 Stephens DS, Farley MM. Pathogenic events during infection of the human nasopharynx with *Neisseria meningitidis* and *Haemophilus influenzae*. *Rev Infect Dis* 1991; **13**: 22–33.
- 55 Jarva H, Ram S, Vogel U, Blom AM, Meri S. Binding of the complement inhibitor C4bp to serogroup B *Neisseria meningitidis*. *J Immunol* 2005; **174**: 6299–307.
- 56 Schneider MC, Exley RM, Chan H, et al. Functional significance of factor H binding to *Neisseria meningitidis*. *J Immunol* 2006; **176**: 7566–75.
- 57 Marra A, Brigham D. *Streptococcus pneumoniae* causes experimental meningitis following intranasal and otitis media infections via a nonhematogenous route. *Infect Immun* 2001; **69**: 7318–25.
- 58 Grandgirard D, Gaumann R, Coulibaly B, et al. The causative pathogen determines the inflammatory profile in cerebrospinal fluid and outcome in patients with bacterial meningitis. *Mediators Inflamm* 2013; 312476.
- 59 Barichello T, Generoso JS, Simoes LR, Elias SG, Quevedo J. Role of oxidative stress in the pathophysiology of pneumococcal meningitis. *Oxid Med Cell Longev* 2013; 371465.

- 60 Wache C, Klein M, Ostergaard C, et al. Myeloid-related protein 14 promotes inflammation and injury in meningitis. *J Infect Dis* 2015; **212**: 247–57.
- 61 Brouwer M, Read RC, van de Beek D. Host genetics and outcome in meningococcal disease: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 262–74.
- 62 Davila S, Wright VJ, Khor CC, et al. Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. *Nat Genet* 2010; **42**: 772–76.
- 63 Adriani KS, Brouwer M, Geldhoff M, et al. Common polymorphisms in the complement system and susceptibility to bacterial meningitis. *J Infect* 2013; **66**: 255–62.
- 64 Brouwer MC, Thwaites G, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet Infect Dis* 2012; **380**: 1684–92.
- 65 Solomon T, Hart I, Beeching N. Viral encephalitis: a clinician's guide. *Pract Neurol* 2007; **7**: 288–305.
- 66 Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. *J Infect* 2011; **64**: 255–62.
- 67 Nemescu RE, Iancu LS, Dorneanu OS, Ursu RG, Doroban CM. Influence of antibiotic therapy prior to admission on the efficacy of classical methods for the diagnosis of meningococcal disease. *Rev Med Chir Soc Med Nat Iasi* 2014; **118**: 497–502.
- 68 Bronska E, Kalmusova J, Dzupova O, Maresova V, Kriz P, Benes J. Dynamics of PCR-based diagnosis in patients with invasive meningococcal disease. *Clin Microbiol Infect* 2006; **12**: 137–41.
- 69 Poppert S, Essig A, Stoeck B, et al. Rapid diagnosis of bacterial meningitis by real-time PCR and fluorescence in situ hybridization. *J Clin Microbiol* 2005; **43**: 3390–97.
- 70 Richardson DC, Louie L, Louie M, Simor AE. Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis. *J Clin Microbiol* 2003; **41**: 3851–53.
- 71 Singhi SG, Mohankumar D, Singhi PD, Sapru S, Ganguly NK. Evaluation of polymerase chain reaction (PCR) for diagnosing *Haemophilus influenzae* b meningitis. *Ann Trop Paediatr* 2002; **22**: 347.
- 72 Balganes M, Lalitha MK, Nathaniel R. Rapid diagnosis of acute pyogenic meningitis by a combined PCR dot-blot assay. *Mol Cell Probes* 2000; **14**: 61–69.
- 73 Elliott I, Dittich S, Paris D, et al. The use of dried cerebrospinal fluid filter paper spots as a substrate for PCR diagnosis of the aetiology of bacterial meningitis in the Lao PDR. *J Clin Microbiol* 2013; **19**: E466–72.
- 74 Boden K, Sachse S, Baier M, et al. 16S rDNA-PCR and sequencing improves diagnosis of bacterial infection of the central nervous system. *Open Crit Care Med J* 2011; **4**: 44–46.
- 75 Abdeldaim GMK, Stralin K, Korsgaard J, Blomberg J, Welinder-Olsson C, Herrmann B. Multiplex quantitative PCR for detection of lower respiratory tract infection and meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. *BMC Microbiol* 2010; **10**: 310.
- 76 Srinivasan L, Pisapia R, Shah S, Halpern C, Harris M. Can broad-range 16S ribosomal ribonucleic acid gene polymerase chain reactions improve the diagnosis of bacterial meningitis? A systematic review and meta analysis. *Ann Emerg Med* 2012; **60**: 609–20.
- 77 Segawa S, Sawai S, Murata S, et al. Direct application of MALDI-TOF mass spectrometry to cerebrospinal fluid for rapid pathogen identification in a patient with bacterial meningitis. *Clin Chim Acta* 2014; **435c**: 59–61.
- 78 Lavezzo E, Toppo S, Franchin E, et al. Genomic comparative analysis and gene function prediction in infectious diseases: application to the investigation of a meningitis outbreak. *BMC Infect Dis* 2013; **13**: 554.
- 79 Jolley KA, Hill DMC, Bratcher HB, et al. Resolution of a meningococcal disease outbreak from whole-genome sequence data with rapid web-based analysis methods. *J Clin Microbiol* 2012; **50**: 3046–53.
- 80 Nagdev KJ, Kashyap RS, Parida MM, et al. Loop-mediated isothermal amplification for rapid and reliable diagnosis of tuberculous meningitis. *J Clin Microbiol* 2011; **49**: 1861–65.
- 81 Kim DW, Kilgore PE, Kim EJ, et al. The enhanced pneumococcal lamp assay: a clinical tool for the diagnosis of meningitis due to *Streptococcus pneumoniae*. *PLoS One* 2012; **7**: e42954.
- 82 Lee D, Kim EJ, Kilgore PE, et al. Clinical evaluation of a loop-mediated isothermal amplification (LAMP) assay for rapid detection of *Neisseria meningitidis* in cerebrospinal fluid. *PLoS One* 2015; **10**: e0122922.
- 83 Kim DW, Kilgore PE, Kim EJ, Kim SA, Anh DD, Seki M. Loop-mediated isothermal amplification assay for detection of *Haemophilus influenzae* type b in cerebrospinal fluid. *J Clin Microbiol* 2011; **49**: 3621–26.
- 84 Bourke TW, McKenna JP, Coyle PV, Shields MD, Fairley DJ. Diagnostic accuracy of loop-mediated isothermal amplification as a near-patient test for meningococcal disease in children: an observational cohort study. *Lancet Infect Dis* 2015; **15**: 552–58.
- 85 Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from acute bacterial meningitis. *QJM* 2005; **98**: 291–98.
- 86 Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; **345**: 1727–33.
- 87 Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **47**: 303–27.
- 88 Solomon T, Michael BD, Smith PE, et al. National ABN/BIA guideline for the management of encephalitis for adults. *J Infect* 2012; **64**: 347–73.
- 89 Chaudhuri A, Martinez-Martin P, Kennedy PG, et al. EFNS guideline on the management of community acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. *Eur J Neurol* 2008; **15**: 649–59.
- 90 Glimåker M, Johansson B, Grindborg Ö, Bottai M, Lindquist L, Sjölin J. Adult bacterial meningitis: earlier treatment and improved outcome following guideline revision promoting prompt lumbar puncture. *Clin Infect Dis* 2015; **60**: 1162–69.
- 91 Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; **23**: 858–83.
- 92 WHO. Antimicrobial resistance: global report on surveillance 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf (accessed June 5, 2015).
- 93 Auburtin M, Wolff M, Charpentier J, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study. *Crit Care Med* 2006; **34**: 2758–65.
- 94 Djukic M, Bottcher T, Wellmer A, et al. Moxifloxacin in experimental *Streptococcus pneumoniae* cerebritis and meningitis. *Neurocrit Care* 2005; **2**: 325–29.
- 95 Sakoulas G, Nonejuie P, Kullar R, Pogliano J, Rybak MJ, Nizet V. Examining the use of ceftaroline in the treatment of *Streptococcus pneumoniae* meningitis with reference to human cathelicidin LL-37. *Antimicrob Agents Chemother* 2015; **59**: 2428–31.
- 96 Sipahi O, Bardak S, Turhan T, et al. Linezolid in the treatment of methicillin-resistant staphylococcal post-neurosurgical meningitis: a series of 17 cases. *Scand J Infect Dis* 2011; **43**: 757–64.
- 97 Fernandez-Ruiz M, Cervera C, Pitart C, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* meningitis complicated by cerebral infarction. Role of antibiotic combination of linezolid plus levofloxacin. *Intern Med* 2010; **49**: 1971–74.
- 98 Vena A, Falcone M, Comandini E, et al. Daptomycin plus trimethoprim/sulfamethoxazole combination therapy in post-neurosurgical meningitis caused by linezolid-resistant *Staphylococcus epidermidis*. *Diagn Microbiol Infect Dis* 2013; **76**: 99–102.
- 99 Kelesidis T, Humphries R, Ward K, Lewinski MA, Yang O. Combination therapy with daptomycin, linezolid, and rifampin as treatment option for MRSA meningitis and bacteremia. *Diagn Microbiol Infect Dis* 2011; **71**: 286–90.
- 100 Knoll BM, Hellmann M, Kotton CN. Vancomycin-resistant *Enterococcus faecium* meningitis in adults: case series and review of the literature. *Scand J Infect Dis* 2013; **45**: 131–39.
- 101 Morelli P, Ferrario A, Tordato F, et al. Successful treatment of post-neurosurgical multidrug-resistant *Pseudomonas aeruginosa* meningo-encephalitis with combination therapy of colistin, rifampicin and doripenem. *J Antimicrob Chemother* 2014; **69**: 857–59.

- 102 European Centre for Disease Prevention and Control. Proportion of penicillin resistant (R) *Streptococcus pneumoniae* isolates in participating countries in 2013. 2013. http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx (accessed Feb 26, 2015).
- 103 Kim SH, Song J-H, Chung DR, et al. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother* 2012; **56**: 1418–26.
- 104 Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. *Clin Infect Dis* 2015; **61**: 767–75.
- 105 Centers for Disease Control. Active Bacterial Core Surveillance. 2014. <http://www.cdc.gov/abcs/reports-findings/survreports/spneu14.html> (accessed Dec 30, 2015).
- 106 Antignac A, Ducos-Galand M, Guiyoule A, Pirès R, Alonso J-M, Taha M-K. *Neisseria meningitidis* strains isolated from invasive infections in France (1999–2002): phenotypes and antibiotic susceptibility patterns. *Clin Infect Dis* 2003; **37**: 912–20.
- 107 Caniça M, Dias R, Nunes B, Carvalho L, Ferreira E, Meningococci Study Group. Invasive culture-confirmed *Neisseria meningitidis* in Portugal: evaluation of serogroups in relation to different variables and antimicrobial susceptibility (2000–2001). *J Med Microbiol* 2004; **53**: 921–25.
- 108 Brown EM, Fisman DN, Drews SJ, et al. Epidemiology of invasive meningococcal disease with decreased susceptibility to penicillin in Ontario, Canada, 2000 to 2006. *Antimicrob Agents Chemother* 2010; **54**: 1016–21.
- 109 Trotter CL, Fox AJ, Ramsay ME, et al. Fatal outcome from meningococcal disease – an association with meningococcal phenotype but not with reduced susceptibility to benzylpenicillin. *J Med Microbiol* 2002; **51**: 855–60.
- 110 Nathan N, Borel T, Djibo A, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet* 2005; **366**: 308–13.
- 111 Molyneux E, Nizami SQ, Saha S, et al. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. *Lancet* 2011; **377**: 1837–45.
- 112 Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta analysis of randomised controlled trials in children. *Arch Dis Child* 2009; **94**: 607–14.
- 113 Ellis-Pegler R, Galler L, Roberts S, Thomas M, Woodhouse A. Three days of intravenous benzyl penicillin treatment of meningococcal disease in adults. *Clin Infect Dis* 2003; **37**: 658–62.
- 114 Skoczynska A, Wasko I, Kuch A, et al. A decade of invasive meningococcal disease surveillance in Poland. *PLoS One* 2013; **8**: e71943.
- 115 Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; **39**: 1267–84.
- 116 McGill F, Heyderman RS, Michael BD, et al. The UK Joint specialist societies guideline on the management of community acquired bacterial meningitis in immunocompetent adults. *J Infect* 2016; **72**: 405–38.
- 117 Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011; **364**: 2016–25.
- 118 Erdem H, Elaldi N, Öztoprak N, et al. Mortality indicators in pneumococcal meningitis: therapeutic implications. *Int J Infect Dis* 2014; **19**: 13–19.
- 119 Bodilsen J, Dalager-Pedersen M, Schonheyder HC, Nielsen H. Dexamethasone treatment and prognostic factors in community-acquired bacterial meningitis: a Danish retrospective population-based cohort study. *Scand J Infect Dis* 2014; **46**: 418–25.
- 120 Domingo P, Pomar V, de Benito N, et al. The spectrum of acute bacterial meningitis in elderly patients. *BMC Infect Dis* 2013; **13**: 108.
- 121 Ajdukiewicz KMB, Cartwright K, Scarborough M, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. *Lancet Infect Dis* 2011; **11**: 293–300.
- 122 Gessner BD, Mueller JE, Seydou Y. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. *BMC Infect Dis* 2010; **10**: 22.
- 123 Scarborough M, Gordon S, Whitty C, et al. Corticosteroids for bacterial meningitis in adults in sub Saharan Africa. *N Engl J Med* 2007; **357**: 2441–50.
- 124 Brouwer MC, McIntyre P, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2013; **6**.
- 125 de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347**: 1549–56.
- 126 Mai N, Chau T, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2004; **357**: 2431–40.
- 127 van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurol* 2010; **9**: 254–63.
- 128 Lepur D, Kutlesa M, Barsic B. Induced hypothermia in adult community-acquired bacterial meningitis - more than just a possibility? *J Infect* 2011; **62**: 172–77.
- 129 Kutlesa M, Lepur D, Barsic B. Therapeutic hypothermia for adult community-acquired bacterial meningitis—historical control study. *Clin Neurol Neurosurg* 2014; **123**: 181–86.
- 130 Mourvillier B, Tubach F, van de Beek D, et al. Induced hypothermia in severe bacterial meningitis. a randomised clinical trial. *JAMA* 2013; **310**: 2174–83.
- 131 Leroux-Roels G, Maes C, De Boever F, Traskine M, Ruggeberg JU, Borys D. Safety, reactogenicity of a novel pneumococcal protein-based vaccine in adults: A phase I/II randomised clinical study. *Vaccine* 2014; **32**: 6838–46.
- 132 Leroux-Roels I, Devaster JM, Leroux-Roels G, et al. Adjuvant system ASO2v enhances humoral and cellular immune responses to pneumococcal protein PhtD vaccine in healthy young and older adults: randomised, controlled trials. *Vaccine* 2015; **33**: 577–84.
- 133 Darrieux M, Goulart C, Briles D, Leite LC. Current status and perspectives on protein-based pneumococcal vaccines. *Crit Rev Microbiol* 2015; **41**: 190–200.
- 134 Oster P, Lennon D, O'Hallahan J, Mulholland K, Reid S, Martin D. MeNZB: a safe and highly immunogenic tailor-made vaccine against the New Zealand *Neisseria meningitidis* serogroup B disease epidemic strain. *Vaccine* 2005; **23**: 2191–96.
- 135 Bjune G, Høiby EA, Grønnesby JK, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 1991; **338**: 1093–96.
- 136 Sierra GV, Campa HC, Varcacel NM, et al. Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. *MPH Annals* 1991; **14**: 195–207.
- 137 Findlow J, Borrow R, Snape MD, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin Infect Dis* 2010; **51**: 1127–37.
- 138 Gossger N, Snape MD, Yu L-M, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; **307**: 573–82.
- 139 Santolaya ME, O'Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet* 2012; **379**: 617–24.
- 140 Read RC, Baxter D, Chadwick DR, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. *Lancet* 2014; **384**: 2123–31.
- 141 Froisi G, Biolchi A, Lo Sapio M, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 2013; **31**: 4968–74.
- 142 Liechti F, Grandgirard D, Leib SL. Bacterial meningitis: insights into pathogenesis and evaluation of new treatment options: a perspective from experimental studies. *Future Microbiol* 2015; **10**: 1195–213.